EXPRESS MAIL NO. EV333997180US		
DECLARATION OF KARL WEISGRABER UNDER 37 C.F.R. § 1.132	Attorney Docket Confirmation No.	UCAL-222 5282
	First Named Inventor	Karl H. Weisgraber
	Application Number	10/017,718
	Filing Date	December 14, 2001
	Group Art Unit	1632
Address to: Commissioner for Patents Alexandria, VA 22313-1450	Examiner Name	T.N. Ton
	Title	*Gene-targeted animal model of apolipoprotein E4 domain interaction and uses thereof*

Dear Sir:

1. I, Karl Weisgraber, declare and say I am a co-inventor of the claims of the above-identified patent application.

2. I have read the Office Action dated April 20, 2004 in this application and understand that the Examiner has rejected pending claims 1, 3, 5, 7, 14, 15, and 20-22 on the basis that, in the words of the April 24, 2004 Office Action, the instant specification fails to provide a correlation between the phenotype of the claimed transgenic mice and Alzheimer's Disease (AD).

3. The following paragraphs describe experiments conducted in my laboratory. The results of the experiments provide further evidence for the fact that a gene-targeted mouse that bears a Thr→Arg substitution at a position equivalent to Arg-61 in human apoE4 exhibits a phenomenon associated with AD, and therefore is suitable for use in identifying agents that reduce a phenomenon associated with AD.

Kainic Acid Injury Model of Neurodegeneration

4. Arginine-61 targeted and wild type mice were injected with kainic acid. Kainic acid is an excitotoxin that crosses the blood-brain barrier and over-stimulates neurons in the hippocampus, resulting in neurodegeneration of these neurons. Presynaptic terminals were quantified in brain sections of each animal five days after injection by synaptophysin immunoreactivity and confocal microscopy to determine neurodegeneration. As shown in Figure 1, provided herewith as Exhibit 2, there was a significantly more neurodegeneration in the arginine-61 mice, compared to the wild type controls.

5. These results parallel those obtained in apoE3 and apoE4 transgenic mice, and are consistent with the conclusion that the arginine-61 mouse apoE mimics human apoE4, and that domain interaction is a major contributor to the neurodegeneration in this standard model of brain injury. This study provides a direct link of apoE domain interaction with neurodegeneration, which is a phenomenon associated with AD.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such will false statements may jeopardize the validity of the application or any patent issuing thereon.

6/28/04
Date

Karl H. Weisgraber
Karl H. Weisgraber

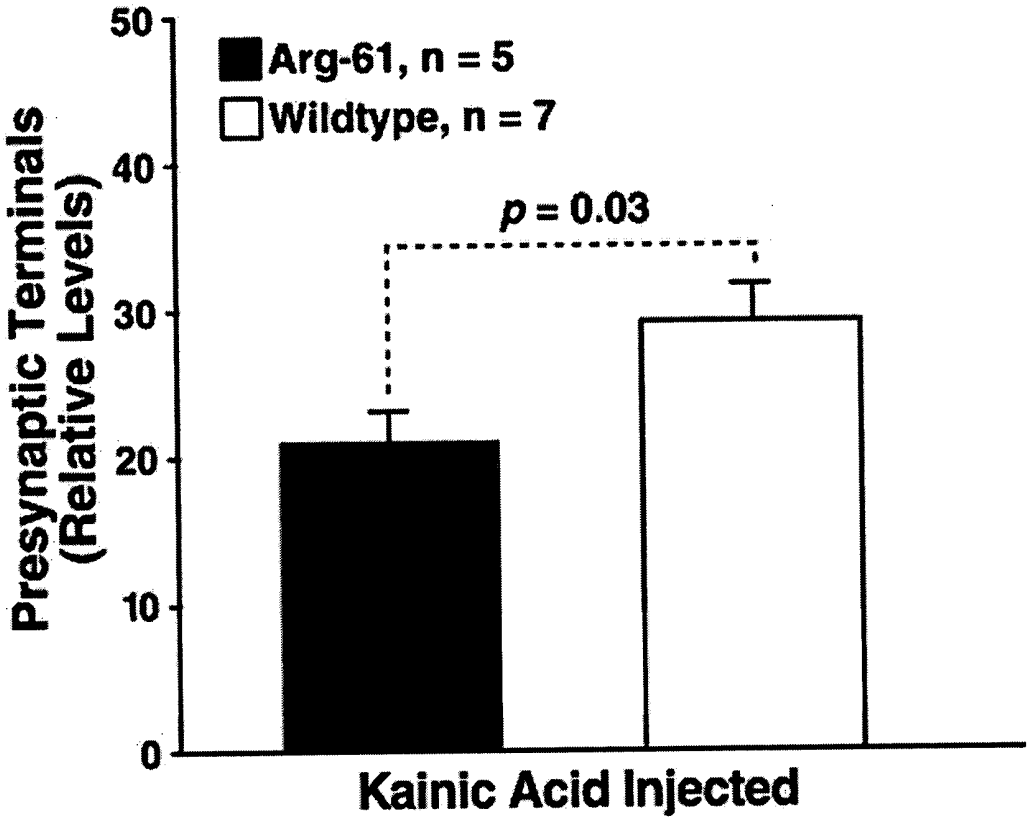

Figure 1

EXPRESS MAIL NO. **EV333997180US**		
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Dear Sir:

1. I, Karl Weisgraber, declare and say I am a co-inventor of the claims of the above-identified patent application. I directed others and personally performed the research leading to the invention disclosed and claimed therein.

2. I have read the Office Action dated April 20, 2004, in this application and understand that the Examiner has rejected pending claims 1, 3, and 5 over Raffai et al. ((October 31, 2000) *Circulation* Vol. 102(18) Suppl. II-150 Abstract No. 729; "the Raffai Abstract").

3. The Raffai Abstract names Robert L. Raffai, Li-Ming Dong, Bryan Tow, Robert V. Farese, and Karl H. Weisgraber as authors. The instant patent application lists Karl H. Weisgraber, Robert V. Farese, Robert L. Raffai, Li-Ming Dong as inventors.

4. Robert V. Farese, Robert L. Raffai, Li-Ming Dong,and I conceived of and reduced to practice the invention disclosed and claimed within this application. Bryan Tow is not an inventor, but was named as a co-author on the Raffai Abstract due to technical contributions he provided. Specifically, Bryan Tow's role was in his position as a Research Associate in the Gladstone Blastocyte Core facility ("the Core facility"). Bryan Tow was given the Arg-61 targeted embryonic stem cells that Dr. Raffai generated, and he implanted the embryonic stem cells into mice as part of his routine responsibilities in the Core facility. Bryan Tow did not provide inventive input with respect to the invention disclosed and claimed in this application.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such will false statements may jeopardize the validity of the application or any patent issuing thereon.

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